

BIOGRAPHICAL SKETCH

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NAME Robert Brenner	POSITION TITLE Associate Professor of Physiology		
eRA COMMONS USER NAME RBrenner			
EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
University of Texas at Arlington, Arlington, TX	B.S.	1982	Microbiology
San Diego State University, San Diego, CA	M.S.	1992	Biology
University of Texas at Austin, Austin, TX	Ph.D.	1997	Biology

A. Personal Statement

The focus of my studies has been to understand how ion channels regulate excitability of cells. My approach is to understand channel regulation *in vitro*, and complement these studies using mouse genetics to understand the physiological consequences of ion channel regulation. My interest in the BK beta4 subunit occurred after our initial cloning of this protein originated from its highly enriched expression in the CNS. We then carefully characterized how this subunit modulates BK channels within the context of the BK channel allosteric gating model in early 2006, and at approximately at the same time generated a gene knockout for the beta4 which revealed temporal lobe, non-convulsive seizures in late 2005. My experimental approaches include molecular and genetic techniques to manipulate channel genes, and the requisite electrophysiology techniques to study their effects in isolated cells (patch and whole cell recording), brain slices (IR imaging and slice electrophysiology) or in the whole animal (behavioral assays and video-EEG monitoring). My major contribution to the epilepsy field has been the detailed understanding of BK channels' effect on intrinsic excitability in dentate gyrus granule neurons, and to show that gain-of-function of BK potassium channels can be pro-excitatory and cause epilepsy. Below are some of our review articles that reflect on our broader understanding of BK channels and their role in epilepsy.

1. Wang B, Jaffe DB, **Brenner R**, Current understanding of iberitoxin-resistant BK channels in the nervous system, *Front Physiol.* 2014 Oct 9;5:382.
2. Wilcox KS and **Brenner R**, Potassium Channelopathies of Epilepsy, *Jaspers Basic Mechanisms of Epilepsy*, Chapter 59, 4th edition, 2012, New York: Oxford University Press.
3. Wang B, Chen QH, **Brenner R**. Proepileptic effects of BK channel gene mutations In: Philip A. Schwartzkroin, Editor. *Encyclopedia of Basic Epilepsy Research*. Elsevier Press; 2009.
4. Petrik D, Chen QH, **Brenner R**, BK Potassium Channel Mutations Affecting Neuronal Function and Epilepsy, In: Scott. C. Baraban, Editor. *Neuromethods, Animal Models of Epilepsy: Methods and Innovations*, May 2009.

B. Positions and Honors**Positions and Employment**

1983 - 1984	Laboratory Technician, City of Dallas Environmental Health Lab, Dallas, TX
1984 - 1987	Research Assistant, San Diego Region Water Reclamation Agency, Santee, CA
1987 - 1990	Research Associate, Salk Institute Biotechnology Industrial Assoc., La Jolla, CA
1991 - 1997	Graduate Research Assistant, University of Texas at Austin, Austin, TX
1998 - 2002	Postdoctoral Research Fellow, Howard Hughes Medical Institute, Stanford University School of Medicine, Stanford, CA
2003- 2008	Assistant Professor of Physiology, University of Texas Health Science Center at San Antonio, San Antonio, TX
2008-	Associate Professor of Physiology, University of Texas Health Science Center at San Antonio, San Antonio, TX

Honors and Awards

1988	Certificate in Recombinant DNA Technology, San Diego State University.
1995	United States Patent #5,407,820 Calcium channel alpha2 subunit DNA's and cells expressing them, M.E. Williams, S.B. Ellis, M.M. Harpold, A. Schwartz and R. Brenner
1995 – 1997	A.D. Hutchison University Fellowship
1996	Carl Gottfried Hartman Fellowship
2008	UT Health Science Center Presidential Junior Scholar Award

C. Contribution to Science

My contribution most relevant to this project is the understanding of how beta4 subunits protect against increases in excitability in dentate gyrus granule neurons and seizures. These studies have converged on a model where fast-gated BK channels and a larger fAHP (through functional coupling with ryanodine receptors as a calcium source) increase spike frequency. Whereas beta4 subunits slow gating of BK channels and prevent these pro-excitatory effects. We have also applied our expertise to understanding the role of adiponectin receptors in affecting dentate gyrus excitability and contextual fear memory.

- a. **Brenner R**, Chen Q, Vilaythong A, Toney G, Noebels JL, Aldrich, RW: BK channel beta4 reduces dentate gyrus excitability and protects against temporal lobe seizures, *Nat Neurosci*, 2005, 8(12):1752-9. PMID: 16261134. □subun
- b. Petrik D, Wang B, **Brenner R**: The modulatory beta4 subunit prevents phosphorylation-dependent activation of BK channels in dentate gyrus granule neurons, *Euro. J. Neurosci.*, 2011, 34:695-704. PMC3168689.
- c. Sonal S, Joanna U, Fitzpatrick J, **Brenner R**, and Bruchez MP, Barth AL: A role for the brain-specific $\beta 4$ subunit in controlling BK channel localization, *PLOS One*, 2012, 7(3):e33429. PMCID: PMC330640.
- d. Zhang D, Wang X, Wang B, Garza J, Fang X, Wang J, Scherer PE, **Brenner R**, Zhang W, Lu XY. 2016. Adiponectin modulates contextual fear extinction and intrinsic excitability of dentate gyrus granule neurons through AdipoR2 receptors, *Molecular Psychiatry*, 2016, May 3.
- e. Wang B, Bugay V, Ling L, Chuang H, Jaffe DB, **Brenner R**, Knockout of the BK $\beta 4$ subunit promotes a functional coupling of BK channels and ryanodine receptors that mediate a fAHP-induced increase in excitability, *J Neurophys*, 2016, 116(2):456-65.

Our studies of BK and beta4 subunits in dentate gyrus granule neurons are also complemented by biophysical studies of these channels in heterologous expression systems (HEK293 cells). These studies allow us to understand the mechanisms by which beta subunits and epilepsy mutations affect BK channel gating properties. By incorporating these data into a dentate gyrus granule neuron computational model we can potentially understanding their effect on neuronal excitability. From initial cloning in 2000 to ongoing biophysical studies and computational modeling, we have made significant headway in understanding how beta4 acts as an inhibitory subunit on BK channel activation during spiking. Our studies also indicate that beta4 subunits also regulate how BK channels respond to phosphorylation regulation.

- a. **Brenner R**, Jegla T, Wickenden Liu AY, Aldrich RW, Cloning and functional characterization of novel large conductance calcium-activated potassium channel beta subunits, hKCNMB3 and hKCNMB4, 2000, *J Biol Chem* 275(9): 6453-6461
- b. Wang B, Rothberg BS, **Brenner R**: Mechanisms of $\beta 4$ subunit modulation of BK channels. *J Gen Physiol.*, 2006, 127(4):449-65. PMCID: PMC2151511
- c. Petrik D and **Brenner R**: Regulation of STREX BK channels by the Accessory Beta4 Subunit. 2007 *Neuroscience*, Nov 23; 149(4):789-803

- d. Wang B, Rothberg BS, **Brenner R**: Mechanism of increased BK channel activation from a channel mutation that causes epilepsy, *J Gen Physiol.*, 2009, 133(3):283-94. PMCID: PMC2654085
- e. Jaffe DB, Wang B, **Brenner R**: How Type I and Type II BK channels differentially shape action potentials, *Neurosci.*, 2011, 192:205-218. PMC3166373.

Other contributions we made to science include our studies of BK channels and accessory beta1 subunits in smooth muscle. Much of this work is related to the role of the related beta1 accessory subunit in vascular and airway smooth muscle. Similar to beta4 studies described above, we have employed both gene knockouts, biophysical studies, and physiological studies (smooth muscle contractility) to demonstrate the key role of the accessory beta1 subunit to increase steady state opening of BK channels, increase functional coupling to ryanodine receptors, reduce resting voltage and relax airway and vascular muscle. In addition, we have identified mutations in the human beta1 subunit that reduce BK channel openings and increases asthma severity.

- a. Brenner R, Perez GJ, Bonev AD, Eckman DM, Kosek JC, Wiler SW, Patterson AJ, Nelson MT, Aldrich RW: Vasoregulation by the beta1 subunit of the calcium-activated potassium channel. *Nature* 2000, 407:870-876. PMID: 11057658.
- b. Semenov I, Wang B, Herlihy JT, Brenner R: BK Channel β_1 Subunit Regulation of Calcium Handling and Constriction in Tracheal Smooth Muscle. *Am J Physiol Lung Cell Mol Physiol*, 2006, 291(14):802-810. PMID: 16632519.
- c. Seibold MA, Wang B, Eng C, Kumar G, Beckman KB, Sen S, Choudhry S, Meade K, Lenoir M, Watson HG, Thyne S, Williams LK, Kumar R, Weiss KB, Grammer LC, Avila PC, Schleimer RP, Burchard EG, and Brenner R: An African-specific functional polymorphism in *KCNMB1* shows sex-specific association with asthma severity, 2008 *Hum Mol Genet*, 17(17):2681-90. PMC2733805.
- d. Semenov I, Wang B, Herlihy JT, Brenner R: BK Channel β_1 Subunits Regulate Airway Contraction Secondary to M2 Muscarinic Acetylcholine Receptor Mediated Depolarization. *J Physiol*. 2011, 589(7):1803-1817. PMC3099031.
- e. Evseev AI, Semenov I, Archer C, Medina J, Dube PH, Shapiro MS, Brenner R, Functional effects of KCNQ K⁺ channels in airway smooth muscle, *Front. Physiology*, 2013, 4:277.

D. Research Support

Ongoing Research Support:

R21-AI13724 Brenner (PI) 05/01/2014 – 04/30/2017 (no cost extension)

SK channel antagonist as novel bronchodilators for asthma

Goals: The major goals of this project are to understand UCL 1684 effect on sarcoplasmic reticulum calcium load and pH, and contractility of airway smooth muscle. As well, the research will conduct *in vivo* animal studies to evaluate UCL 1684 for effects on airway resistance in asthma.

Role: PI

NSF 1456862 Brenner (PI) 07/01/2015 – 06/30/2018

Understanding How BK Potassium Channels enhance a Neuron's Input/Output Function

Goals: This research proposal will be to understand how BK potassium channels promote an increased excitability in dentate gyrus granule neurons

Role: PI

Department of Defense Shapiro (PI) 09/01/2015 – 08/30/2018

Novel Strategies Targeting Signaling Molecules of Neurons and Astrocytes to Prevent Acquired Epilepsies

Goals: This research proposal will be to investigate how purinergic receptors and KCNQ channels may be pharmacological targets to prevent traumatic brain injury-induced epilepsy and associated comorbidities.

Role: Coinvestigator

Completed Research Support (last 3 years):

R01 NS052574 Brenner (PI) 04/01/07 – 03/31/13 (no-cost extension)

BK Channel B4 Subunit in the Dentate Gyrus and Seizures

The aims of this proposal are to understand how BK channels, and modulation of BK channels by the beta4 subunit regulates the intrinsic excitability properties of hippocampus dentate gyrus granule (DG) cells. Our aims are to identify the calcium sources that activate BK channels, and their consequences on action potential firing. In addition, we will characterize phosphorylation signaling cascades that alter BK channel's affect on excitability of DG neurons.

Role: PI

Morrison Trust Brenner (PI) 10/01/12 – 09/31/13

Novel potassium channel activators as bronchodilators for asthma

Our goal in this proposal is to translate our knowledge of potassium channels in airway smooth muscle to investigate their potential as novel bronchodilators for asthma. We will test two potassium channel agonists, the BK channel agonist BMS191011 and the KCNQ channel agonist Retigabine which has already passed clinical trials and are approved for treatment of epilepsy.

Role: PI

Research Program: My research efforts have focused cellular excitability in neurons and muscle. My research has been to understand how ion channels regulate excitability in disease, and normal function of cells. Students coming to my lab will have the choice of selecting any one of these major projects.

Airway/Lung studies

Currently there is only one class of compound, beta2 agonists, are used as a rescue inhaler for asthma. Unfortunately, with chronic use this compound may lose its effectiveness. We are studying novel bronchodilators to be used for asthma. We conduct calcium imaging studies, airway muscle contraction, and whole animal plethysmography in mice to characterize novel airway smooth muscle relaxants. We have identified a novel class of compound that is very potent, and hopefully can be used as an alternative bronchodilator. However, we need a student to conduct experiments to identify its mechanism of action. The student would conduct calcium imaging studies, and muscle contractility studies to determine its mechanism of action. The success of this project will validate a new bronchodilator for individuals suffering from asthma and COPD.

Changes in ion channels following seizures and fear memory

We are studying the role of a novel protein, the beta4 subunit of BK channels that regulates excitability of neurons. We find that this protein is strongly downregulated following seizures, and also during fear memory. We are generating a novel transgenic mouse that prevents beta4 downregulation to determine if this is an important process for epilepsy development and fear memory. The student would conduct EEG recordings, and behavioral studies of fear memory in mice to understand the role of the beta4 protein. Also, the student will also use the DREADD technology to activate dentate gyrus hippocampus neurons to evaluate this brain region in beta4 activity dependent regulation. The success of these studies will characterize a new plasticity mechanism that regulates neuronal excitability.

Understanding traumatic brain injury

Head trauma is a leading cause of epilepsy development. We are currently studying the mechanisms of neuronal changes leading from acute trauma to epilepsy development. We are using a novel cellular reporter that generates red-fluorescent protein expression in those neurons where neuronal activity is increased in vivo, in mice. Using this so called "TRAP" reporter, we hope to identify those brain regions, and specific neuronal types, that are sensitive to traumatic brain injury and respond by maladaptive increases in neuronal activity. Once these brain regions are identified, the student will target these regions for focal EEG recordings, and also for electrophysiology, to determine how their neuronal activity changes. Further, we will employ delivery of novel drugs that reduce neuronal activity in those regions to prevent the development of epilepsy. The success of these studies will determine the mechanism of post-traumatic epilepsy, and perhaps also find some potential cures.